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AUG 01 2002

510(k) Summary of Safety and Effectiveness

HerpeSelect®2 ELISA IgG Catalog No. EL0920G
Prepared July 23, 2002

Applicant Focus Technologies, Inc.
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Establishment Registration No. 2023365

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Summary Date July 23, 2002

Proprietary Name HerpeSelect®2 ELISA IgG (automated option)

Generic Name HSV-2 ELISA IgG

Classification Herpes Simplex Virus Serological Reagents
21 CFR §866.3305
Class III

Predicate Device HerpeSelect®2 ELISA IgG (manual option)

Device Description
In the HerpeSelect®2 ELISA IgG assay, the polystyrene microwells are coated with recombinant gG-2 antigen. Diluted serum samples and controls are incubated in the wells to allow specific antibody present in the samples to react with the antigen. Nonspecific reactants are removed by washing, and peroxidase-conjugated anti-human IgG is added and reacts with specific IgG. Excess conjugate is removed by washing. Enzyme substrate and chromogen are added, and the color is allowed to develop. After adding the Stop Reagent, the resultant color change is quantified by a spectrophotometric reading of optical density (OD). Sample optical density readings are compared with reference cut-off OD readings to determine results.

Intended Use
Focus Technologies' HerpeSelect® 2 ELISA IgG test is intended for qualitatively detecting the presence or absence of human IgG class antibodies to HSV-2 in human sera. In conjunction with the Focus HerpeSelect® 1 ELISA IgG, the test is indicated for testing sexually active adults or expectant mothers for aiding in the presumptive diagnosis of HSV infection. The assay can be used manually or in conjunction with an automated system as outlined in the package insert. **The user is responsible for assay performance characteristics when an automated system is used.** The performance of this assay has not been established for use in a pediatric population, for neonatal screening, or for testing of immunocompromised patients.

EXPECTED VALUES

An outside investigator assessed the device with masked, archived and unselected sera from 1) sexually active adults over the age of 14 (n = 246), and 2) from expectant mothers (n = 241). The reference method was a HSV-2 Western blot from a Pacific Northwest university. The observed prevalences and the hypothetical predictive values for the two populations are shown in the tables below. The positive predictive value will decrease proportionally to the prevalence of HSV infection as reflected in the table below. The calculations are based on HerpeSelect® 2 ELISA IgG having

1) a hypothetical sensitivity of 96.1% & a hypothetical specificity of 97.0% (sexually active adults), and
2) a hypothetical sensitivity of 100% and a hypothetical specificity of 96.1% (expectant mothers).

Observed Prevalence with Sexually Active Adults & Expectant Mothers

Population	HSV-2 Serostatus	Observed Prevalence	
		WB	Focus ELISA
Sexually Active Adults *	neg	68.5%	67.2%
	+	31.5%	32.4%
Expectant Mothers †	neg	75.6%	72.3%
	+	24.4%	27.3%

* Excludes 5 atypical Western blots and 1 ELISA equivocal.
† Excludes 3 atypical Western blots and 1 ELISA equivocal.

Prevalence vs. Hypothetical Predictive Values

Prevalence	Sexually Active Adults		Expectant Mothers	
	PPV	NPV	PPV	NPV
50%	97.0%	97.0%	96.2%	96.1%
40%	95.5%	98.0%	94.5%	97.4%
30%	93.2%	98.7%	91.7%	98.3%
25%	91.4%	99.0%	89.5%	98.7%
20%	88.9%	99.2%	86.5%	99.0%
15%	85.0%	99.5%	81.9%	99.3%
10%	78.1%	99.7%	74.0%	99.6%
5%	62.8%	99.8%	57.4%	99.8%

Note: Sexually active adult and expectant mother populations in different geographic areas may produce different frequency distributions from the table above. Each laboratory should establish frequency distributions for their specific patient populations.

PERFORMANCE CHARACTERISTICS

Relative Sensitivity and Relative Specificity with Expectant Mothers †

An outside investigator assessed the device's relative sensitivity and relative specificity with sera from expectant mothers (n = 241). The sera were sequentially submitted to the laboratory, archived, and masked. The reference method was a HSV-2 Western blot (WB) from a Pacific Northwest university. Of 3 atypical Western blots, HerpeSelect® 2 ELISA IgG (EL) was 1 equivocal and 2 negatives. Of 58 Western blot positives, HerpeSelect® 2 ELISA IgG was 58 positive. Of 180 Western blot negatives, HerpeSelect® 2 ELISA IgG was 172 negatives, 7 positives, and 1 equivocal.

Relative Sensitivity and Relative Specificity with Expectant Mothers (n = 241) †

Characteristic	% (EL/WB)*	95% CI
Sensitivity relative to Western blot	100% (58/58)	93.8-100%
Specificity relative to Western blot	96.1% (172/179)	92.1-98.4%

* Excludes three atypical Western blots and one ELISA equivocal

† The word "relative" refers to comparing this assay's results with those of a similar assay. No attempt was made to correlate the assay results to disease presence or absence. No judgment can be made on the similar assay's accuracy in predicting disease. Assay performed by manual method.

Relative Sensitivity and Relative Specificity with Sexually Active Adults †

An outside investigator assessed the device's relative sensitivity and relative specificity with sera from sexually active adults over the age of 14 (n = 246). The sera were sequentially submitted to the laboratory, archived, and masked. The reference method was a HSV-2 Western blot from a Pacific Northwest university. Of 5 atypical Western blots, HerpeSelect® 2 ELISA IgG was 2 equivocal, 2 negative and 1 positive. Of 76 Western blot positives, HerpeSelect® 2 ELISA IgG was 73 positive and 3 negative. Of 165 Western blot negatives, HerpeSelect® 2 ELISA IgG was 159 negative, 5 positive, and 1 equivocal.

Relative Sensitivity and Relative Specificity with Sexually Active Adults (n = 246) †

Characteristic	% (EL/WB)*	95% CI
Sensitivity relative to Western blot	96.1% (73/76)	88.9-99.2%
Specificity relative to Western blot	97.0% (159/164)	93.0-99.0%

* Excludes five atypical Western blots and one ELISA equivocal

† The word "relative" refers to comparing this assay's results with those of a similar assay. No attempt was made to correlate the assay results to disease presence or absence. No judgment can be made on the similar assay's accuracy in predicting disease. Assay performed by manual method.

Relative Sensitivity with Culture Positives †

An outside investigator assessed the device's relative sensitivity using sera from culture positive patients (n = 63). Reference methods included culture (infection) and a HSV-2 Western blot (antibody) from a Pacific Northwest university. Of 5 atypical Western blots, HerpeSelect®2 ELISA IgG was 2 equivocal, 2 negative and 1 positive. Of 63 culture positives, HerpeSelect® 2 ELISA IgG was 61 positive and 2 negative, and Western blot was 62 positive and 1 negative. Of 62 Western blot positives, HerpeSelect® 2 ELISA IgG was 61 positive and 1 negative.

Relative Sensitivity with Culture Positives (n = 63) †

Characteristic	% (EL/WB or Culture)	95% CI
Sensitivity relative to culture	96.8% (61/63)*	89.0-99.6%
Sensitivity relative to Western blot	98.4% (61/62)*	91.3-100%

*Of the 2 ELISA negatives, one was WB positive and the other WB negative.

† The word "relative" refers to comparing this assay's results with those of a similar assay. No attempt was made to correlate the assay results to disease presence or absence. No judgment can be made on the similar assay's accuracy in predicting disease. Assay performed by manual method.

Agreement with CDC Panel †

The following information is from a serum panel obtained from the CDC and tested by Focus Technologies. The results are presented as a means to convey further information on the performance of this assay with a masked, characterized serum panel. This does not imply an endorsement of the assay by the CDC. The panel consists of 37% positive and 63% negative samples. The HerpeSelect® 2 ELISA IgG demonstrated 100% total agreement with the CDC results. Of the results obtained by Focus Technologies, there was 100% agreement with the positive specimens and 100% agreement with the negative specimens.

† Assay performed by manual method.

Relative Specificity with a Low Prevalence Population †

An outside investigator assessed the device's relative specificity using sera from a population of college students claiming to lack sexual experience (n = 81), and having a published HSV-2 antibody prevalence of 2% (4/186).** The laboratory reference method was a HSV-2 Western blot from a Pacific Northwest university. One atypical Western blot was an HerpeSelect® 2 ELISA IgG negative. Of 78 Western blot negatives, HerpeSelect® 2 ELISA IgG was 77 negative and 1 positive. Of 2 Western blot negatives, HerpeSelect® 2 ELISA IgG was 2 positive.

Relative Specificity with a Low Prevalence Population (n = 81) †

Characteristic	% (EL/WB)*	95% CI
Specificity relative to Western blot†	98.7% (77/78)	93.1-100%
Sensitivity relative to Western blot†	100% (2/2)	15.8-100%

* Excludes one atypical Western blot.

** Corey, L., A. Wald, New Developments in the Biology of Genital Herpes, in Clinical Management of Herpes Viruses, p.46.

† The word "relative" refers to comparing this assay's results with those of a similar assay. No attempt was made to correlate the assay results to disease presence or absence. No judgment can be made on the similar assay's accuracy in predicting disease. Assay performed by manual method.

Type Specificity with HSV-1 Western Blot Positives †

An outside investigator assessed the device's type specificity using HSV-1 Western blot positive and HSV-2 Western Blot negative sera from the above described populations (n = 287): expectant mothers, sexually active adults, low prevalence persons, and HSV-1 culture positives. Of 287 HSV-1 Western blot positive and HSV-2 Western blot negative samples, HerpeSelect® 2 ELISA IgG was 276 negatives, 1 equivocal and 10 positives.

Type Specificity with HSV-1 Western Blot Positives (n = 287) †

Characteristic	% (EL/WB)*	95% CI
Type-specificity relative to Western blot	96.5% (276/286)	93.7-98.3%
Type cross-reactivity relative to Western blot	3.5% (10/286)	1.7-6.3%

* Excludes one equivocal ELISA result.

† The word "relative" refers to comparing this assay's results with those of a similar assay. No attempt was made to correlate the assay results to disease presence or absence. No judgment can be made on the similar assay's accuracy in predicting disease. Assay performed by manual method. Assay performed by manual method.

Cross-reactivity with Taxonomically Related Viruses †

Focus Technologies assessed the device's cross-reactivity using sera (n = 27) from 1) HSV sero-negative by another manufacturer's FDA cleared HSV ELISAs, and 2) IFA IgG positive for taxonomically similar viruses including CMV, EBV VCA, HHV6 and VZV. Discrepants between the FDA cleared HSV ELISAs and the HerpeSelect® 2 ELISA IgG were analyzed using a type specific Western blot from a major university located in the Northwestern United States.

Cross-reactivity with Taxonomically Related Viruses (n = 27) †

IFA IgG Pos	% Agreement Negative*	95% CI
CMV	91.7% (11/12)	61.5-99.8%
EBV VCA	90.9% (20/22)	70.8-98.9%
HHV6	90.9% (20/22)	70.8-98.9%
VZV	90.5% (19/21)	69.6-98.8%
Total	90.9% (70/77)	82.2-96.3%

* Excludes 3 Western blot positives, and one discrepant that was not analyzed with the Western blot because of insufficient volume

† Assay performed by manual method.

Intra-assay & Inter-assay Reproducibility †
An internal investigator assessed the device's intra-assay and inter-assay reproducibility by assaying seven samples in duplicate, twice a day, for twenty days, for a total of forty runs. Two sets of samples were masked duplicates.

Inter-lot Reproducibility †
An internal investigator assessed the device's inter-lot reproducibility. Five samples were run on three separate days with three separate lots. For one lot, the samples were run in triplicate, and run in duplicate with the other two lots. Each of the three lots had a different lot of Antigen Wells.

Inter-laboratory Reproducibility †
An internal investigator and two off-site laboratories assessed the device's inter-laboratory reproducibility. Each of the three laboratories ran seven samples in triplicate on three different days. Three points were excluded because an incorrect sample (instead of sample 27) was run one day.

Reproducibility †

Sample	Inter- & Intra-assay			Inter-lot		Inter-Laboratory		
	Index Mean	Intra-assay %CV	Inter-assay %CV	Index Mean	Index %CV	Index Mean	%CV of Lab Means	Mean of Lab %CVs
21*	0.2	20.5	15.9	0.3	52.4	0.2	19.6	17.3
26*	0.2	12.2	12.4	NA	NA	0.3	33.1	20.7
22**	1.2	6.3	6.2	1.2	5.1	1.2	3.9	7.8
27**	1.2	5.2	6.3	NA	NA	1.1	14.1	8.8
23	1.8	4.7	5.5	1.8	5.4	1.7	5.2	7.
24	3.4	3.2	7.9	3.2	16.7	2.8	11.0	10.8
25	8.2	3.0	6.9	8.0	7.4	6.8	18.6	4.5

* #21 & #26 are same material.
** #22 & #27 are same material.
† Assay performed by manual method.

% Agreement between the Manual and Automated Methods (n = 257)

An internal and an external investigator compared % agreement between the HerpeSelect automated method vs. the manual method as part of a CLIA validation for a major clinical laboratory located in Southern California. The external investigator sequentially selected and manually tested 257 samples. Each sample was from an adult, and was submitted for HSV testing. 255 samples were from the US, and two samples from outside the US. Of the 257 samples, the manual method detected 175 negatives, 3 equivocals, and 79 positives. Of the 175 negatives by the manual method, the automated method agreed with 99.4% (174/175). Of the 3 equivocals by the manual method, the automated method agreed with 0% (0/3). Of the 79 positives by the manual method, the automated method agreed with 98.7% (78/79). Overall, the two methods agreed 98.1% (252/257). Of the five discrepants, two resolved in favor of the automated method, and the other three did not resolve.

% Agreement between Manual and Automated Methods

Interpretation*	% Agreement	95% CI
Negative	99.4% (174/175)	96.4-100%
Equivocal	0.0% (0/3)	0.0-70.8%
Positive	98.7% (78/79)	93.1-100%
Overall	98.1% (252/257)	95.5-99.4%

* Interpretation by manual method.

Reproducibility Using an Automated Instrument

An internal investigator assessed the device's inter-assay and intra-assay reproducibility with an automated instrument. Ten samples were tested in triplicate on three different days. The manual and automated methods agreed 98.9% (89/90). One point from Sample 3 was an outlier (162 standard deviations from the mean).

Sample	Mean Index	Intra-assay %CV	Inter-assay %CV
6	0.06	27.2	20.8
3 (without outlier)*	0.45	8.8	4.6
8	0.10	28.3	25.2
3 (with outlier)*	1.18	51.4	105.4
10	1.39	6.0	5.5
9	1.87	4.8	2.5
5	5.23	2.8	0.9
1	6.38	1.3	3.5
4	7.14	3.0	3.3
7	7.97	6.4	10.8
2	8.21	0.8	4.6

*One point from Sample 3 was an outlier (162 standard deviations from the mean).

Stability after Opening Reagents

An internal investigator assessed stability after the reagents had been opened and used with an automated instrument. The kit was used in the inter-assay/intra-assay reproducibility study (above), re-closed, stored at 2-8C for at least 30 days, and then used again to re-test the same samples. There was 100% agreement with the index when the reagents were opened.

Stability after Opening Reagent

Sample	Index when Opened	After at Least 30 Days (Run 1)	After at Least 30 Days (Run 2)
6	0.06	0.06	0.07
3 (without outlier)	0.45*	0.43	0.48
8	0.10	0.14	0.10
10	1.39	1.60	1.76
9	1.87	2.03	2.11
5	5.23	5.13	5.10
1	6.38	6.79	6.57
4	7.14	7.67	7.26
7	7.97	8.16	8.29
2	8.21	8.38	8.35

*One point from Sample 3 was an outlier, it was 162 SDs from the mean. The values without the outlier are used here.

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
2098 Gaither Road
Rockville MD 20850

AUG 0 1 2002

Michael J. Wagner, Esq.
Senior Regulatory Affairs Specialist
Focus Technologies, Inc.
10703 Progress Way
Cypress, CA 90630

Re: K021486
Trade/Device Name: HerpeSelect ™ 2 ELISA IgG
Regulation Number: 21 CFR 866.3305
Regulation Name: Herpes Simplex Virus Serological Reagents
Regulatory Class: Class III
Product Code: MXJ
Dated: May 2, 2002
Received: May 3, 2002

Dear Mr. Wagner:

We have reviewed your Section 510(k) premarket notification of intent to market the device referenced above and have determined the device is substantially equivalent (for the indications for use stated in the enclosure) to legally marketed predicate devices marketed in interstate commerce prior to May 28, 1976, the enactment date of the Medical Device Amendments, or to devices that have been reclassified in accordance with the provisions of the Federal Food, Drug, and Cosmetic Act (Act) that do not require approval of a premarket approval application (PMA). You may, therefore, market the device, subject to the general controls provisions of the Act. The general controls provisions of the Act include requirements for annual registration, listing of devices, good manufacturing practice, labeling, and prohibitions against misbranding and adulteration.

If your device is classified (see above) into either class II (Special Controls) or class III (PMA), it may be subject to such additional controls. Existing major regulations affecting your device can be found in the Code of Federal Regulations, Title 21, Parts 800 to 898. In addition, FDA may publish further announcements concerning your device in the Federal Register.

Please be advised that FDA's issuance of a substantial equivalence determination does not mean that FDA has made a determination that your device complies with other requirements of the Act or any Federal statutes and regulations administered by other Federal agencies. You must comply with all the Act's requirements, including, but not limited to: registration and listing (21 CFR Part 807); labeling (21 CFR Part 801); good manufacturing practice requirements as set forth in the quality systems (QS) regulation (21 CFR Part 820); and if applicable, the electronic product radiation control provisions (Sections 531-542 of the Act); 21 CFR 1000-1050.

This letter will allow you to begin marketing your device as described in your 510(k) premarket notification. The FDA finding of substantial equivalence of your device to a legally marketed predicate device results in a classification for your device and thus, permits your device to proceed to the market.

If you desire specific advice for your device on our labeling regulation (21 CFR Part 801 and additionally 809.10 for in vitro diagnostic devices), please contact the Office of Compliance at (301) 594-4588. Additionally, for questions on the promotion and advertising of your device, please contact the Office of Compliance at (301) 594-4639. Also, please note the regulation entitled, "Misbranding by reference to premarket notification" (21CFR 807.97). Other general information on your responsibilities under the Act may be obtained from the Division of Small Manufacturers International and Consumer Assistance at its toll-free number (800) 638-2041 or (301) 443-6597 or at its internet address "http://www.fda.gov/cdrh/dsma/dsmamain.html".

Sincerely yours,

Steven Gutman

Steven I. Gutman, M.D., M.B.A.
Director
Division of Clinical Laboratory-Devices
Office of Device Evaluation
Center for Devices and
Radiological Health

Enclosure

510(k) Number (if known): K021486

Device Name:

HerpeSelect® 2 ELISA IgG

Indications for Use:

Focus Technologies' HerpeSelect® 2 ELISA IgG test is intended for qualitatively detecting the presence or absence of human IgG class antibodies to HSV-2 in human sera. In conjunction with the Focus HerpeSelect® 1 ELISA IgG, the test is indicated for testing sexually active adults or expectant mothers for aiding in the presumptive diagnosis of HSV infection. The assay can be used manually or in conjunction with an automated system as outlined in the package insert. **The user is responsible for assay performance characteristics when an automated system is used**. The performance of this assay has not been established for use in a pediatric population, for neonatal screening, or for testing of immunocompromised patients.

(PLEASE DO NOT WRITE BELOW THIS LINE CONTINUE ON ANOTHER PAGE IF NEEDED)

Concurrence of CDRH, Office of Device Evaluation (ODE)

Woody Dubois

(Division Sign-Off)
Division of Clinical Laboratory Devices
510(k) Number K021486

FOR PRESCRIPTION USE X

(Optional Format 3-10-98)